Tafamidis Meglumine
NDA 202737

Transthyretin Familial Amyloid Polyneuropathy

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- To be approved, orphan drugs, like any drug, need substantial evidence of efficacy
  - 2 positive studies, *or*
  - 1 very persuasive study + confirmatory evidence
- Tafamidis: one controlled trial
- FDA is committed to flexibility applying statutory requirements for orphan drugs

Guidance for Approval Based on One Study + Confirmatory Evidence*

Should Have Several Strengths

- Very persuasive p-value
- Few or no negative endpoints
- Evidence in >1 patient group (mutation, country of origin)
- Still evidence of efficacy if eliminate any single site

But No Serious Weaknesses

"…little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol."

**FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998*

Tafamidis Controlled Trial, 005

- Co-primary endpoint: NIS-LL + Norfolk
  - Study positive only if p-value for both < 0.05
    - Small changes in NIS-LL exam by physician may not actually represent improved function of patient
    - Norfolk intended to confirm change has clinical effect

NIS-LL **p = 0.07**

Norfolk **p = 0.12**

Considering other endpoints or other statistical analyses of the primary endpoint when $p > 0.05$ increases risk of concluding a drug is effective when it is not, in ways that can not be quantified

Study quickly ceases to be adequate and well-controlled, or capable of providing reliable evidence

Sensitivity analysis to explore robustness of primary endpoint, not to replace primary endpoint

Sensitivity Analysis Considering Only Patients Completing Study

	ITT population		Efficacy Evaluable*	
	Tafamidis N = 64	Placebo N = 61	Tafamidis N = 45	Placebo N = 42
NIS-LL	p = 0.07		**p = 0.04**	
Norfolk	p = 0.12		**p = 0.05**	

*Patients who had non-missing month 18 NIS-LL and TQOL scores, who took at least 80% of prescribed study medication, and who had no major protocol violations

Sensitivity Analysis Considering Baseline Disease Severity

- Baseline NIS-LL correlated with response
- Including NIS-LL as covariate was a pre-specified sensitivity analysis

NIS-LL **p = 0.16**

Study 005 Weaknesses: Baseline Imbalances

- NIS-LL less severe (2 points) in tafamidis arm, despite 12-month longer symptom duration
- *Concern that, despite randomization, prognosis of tafamidis arm better than placebo arm*
- P-value of imbalances means problems like this not unusual, does not address if affected result
- Must weigh size and implications of imbalance vs. size and implications of result at study end
  - 2.5-point difference between arms at 18 months

Study 005 Weaknesses

- Single site in Portugal provided 58% of patients
  - Onset age and course of FAP due to V30M surprisingly different across populations

"Results obtained in a single center may be dependent on site or investigator-specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population"*

**FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998*

Study 005 Weaknesses

- No evidence of efficacy from other sites combined when exclude single largest site

> "If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished"*

**FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998*

Secondary Endpoints
Study 005

Study 005 Weaknesses

- No prospective plan to control Type 1 error
  - This part of study not ‘adequate and well controlled’
- ‘Statistical significance’ does not apply to ‘nominal’ p-values
  - With multiple-testing, small p-values happen by chance
- Only striking differences that wouldn’t require statistics to interpret might be reliable

- Large nerve fiber endpoint
  - Nominal p-value 0.06
- Small nerve fiber function
  - Nominal p-value 0.005

Worsening of small fiber endpoint in open-label extension

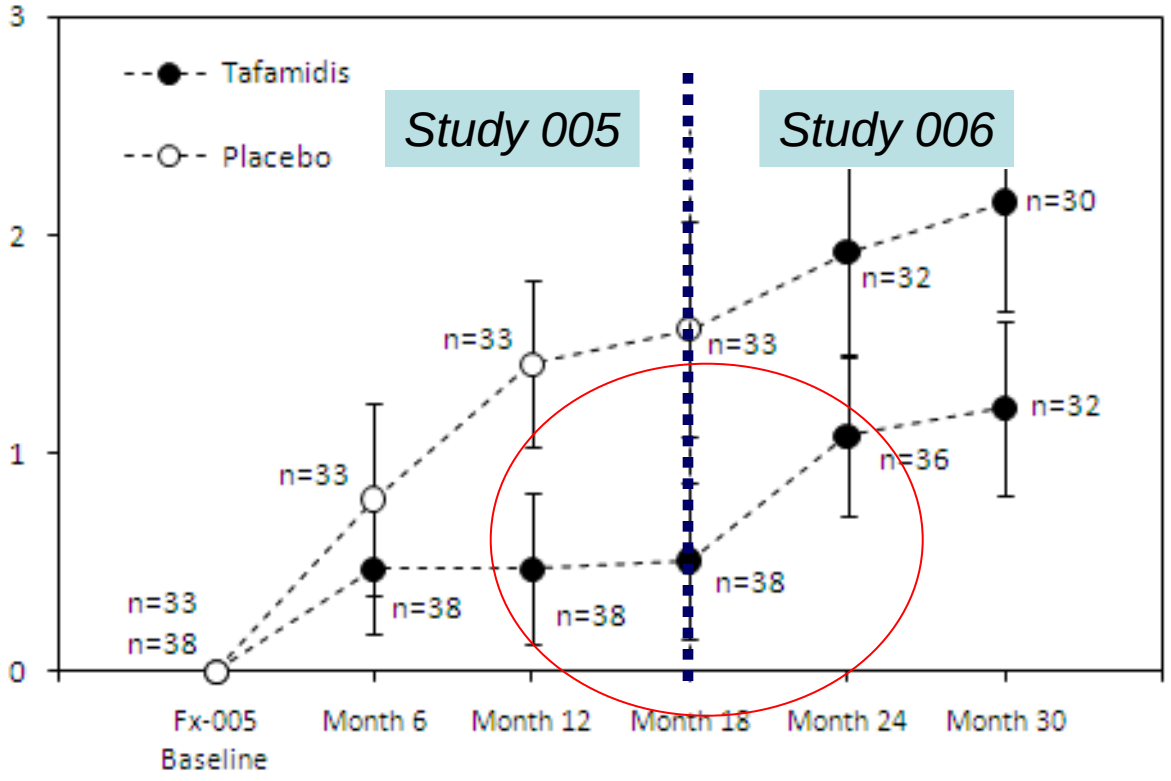

Figure from sponsor efficacy summary

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Modified Body Mass Index (mBMI)

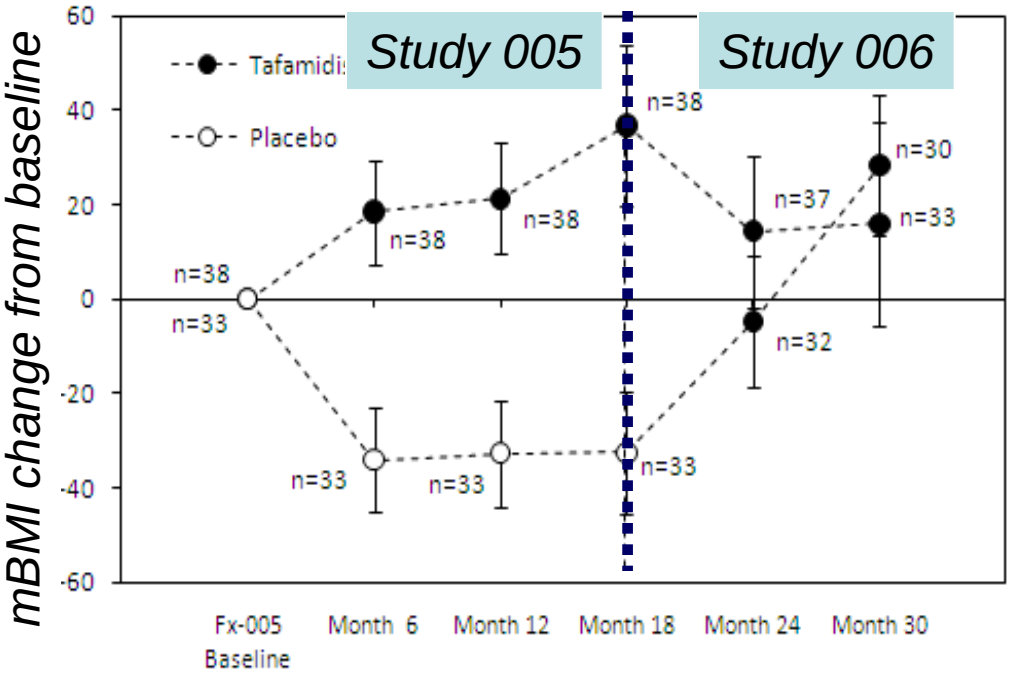
Intended to measure nutritional status

– adjust for edema due to low albumin

mBMI = (Albumin) x (Body Mass Index [BMI])

BMI = body weight/height^2

- mBMI change may be real, but meaning not clear to FDA
- Many drugs change weight without changing nutritional status (e.g. salt)



- Albumin assays can be inaccurate due to albumin oxidation status, glycation, multimeric complexing, levels of other proteins
- Tafamidis binds to albumin, and appears to increase blood level of TTR

Figure from sponsor efficacy summary

Open-Label Data
Study 006

Study 006

- *Not* an adequate and well-controlled trial capable of providing primary support for approval

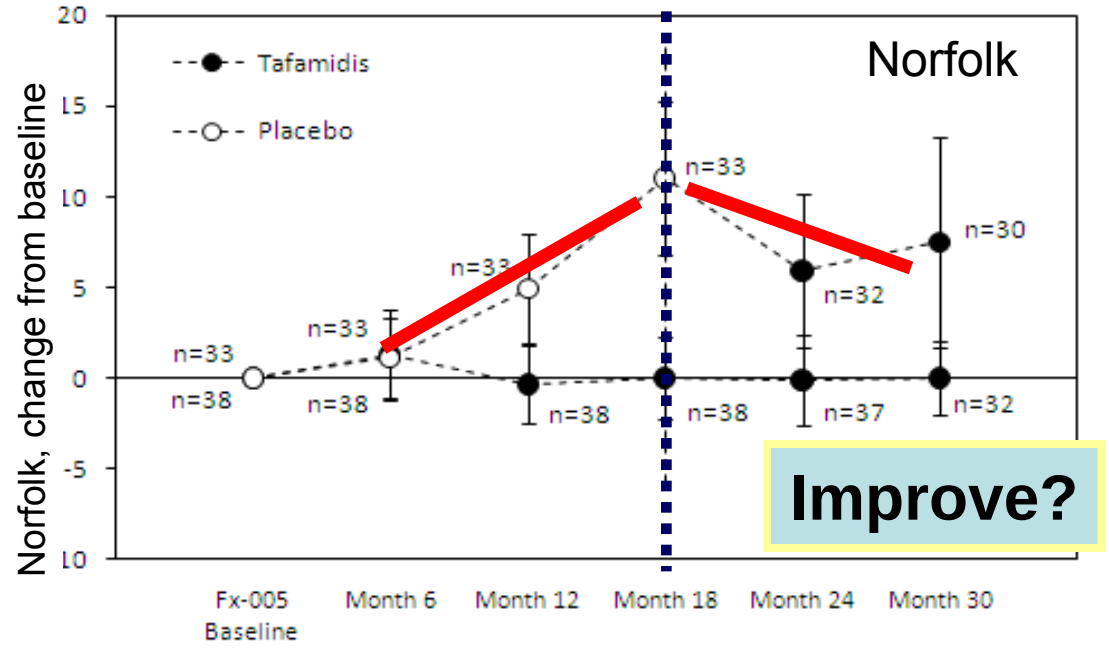
- If combined with a controlled study with very persuasive efficacy findings, could consider if study 006 provided confirmatory evidence to support single-study approval

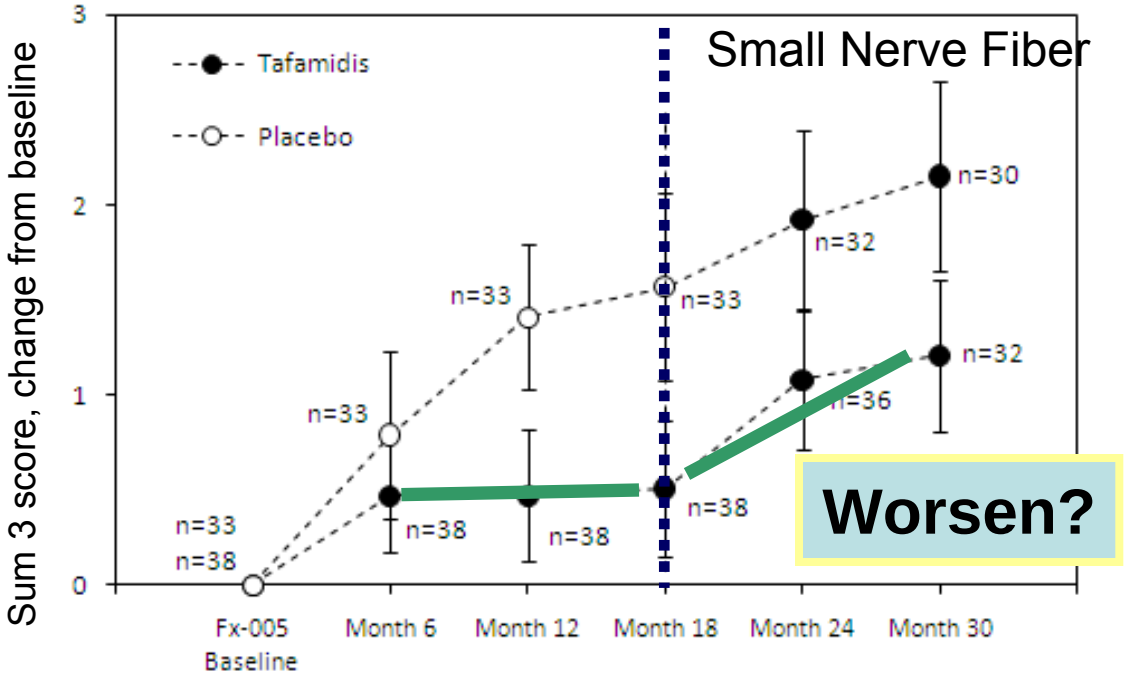
Study 006

- Open-label
- Non-randomized population, dropouts
  - Study arms appear to differ at 006 start, confounding statistical interpretation
- Many endpoints tested
- Endpoints not analyzed in an ordered way that allows control of false-positive findings
- Continuation of study 005
  - not like ‘independent confirmation’
  - Some endpoints in 006 examined entire 30-month period and reflect changes in 005

Not clear to FDA that interpretable pattern emerged in study 006

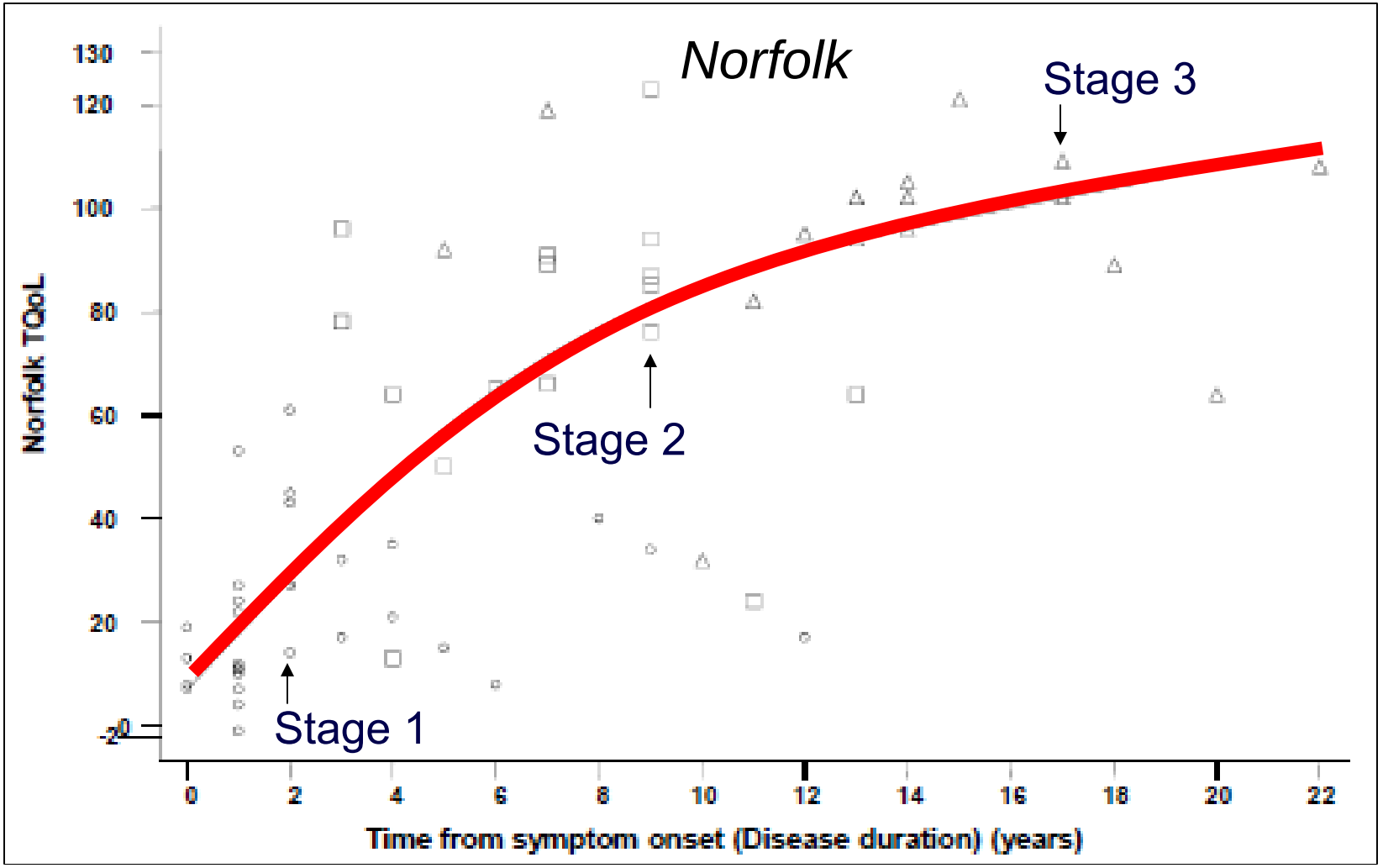
…or what pattern expected as disease progresses





Figures from sponsor efficacy summary

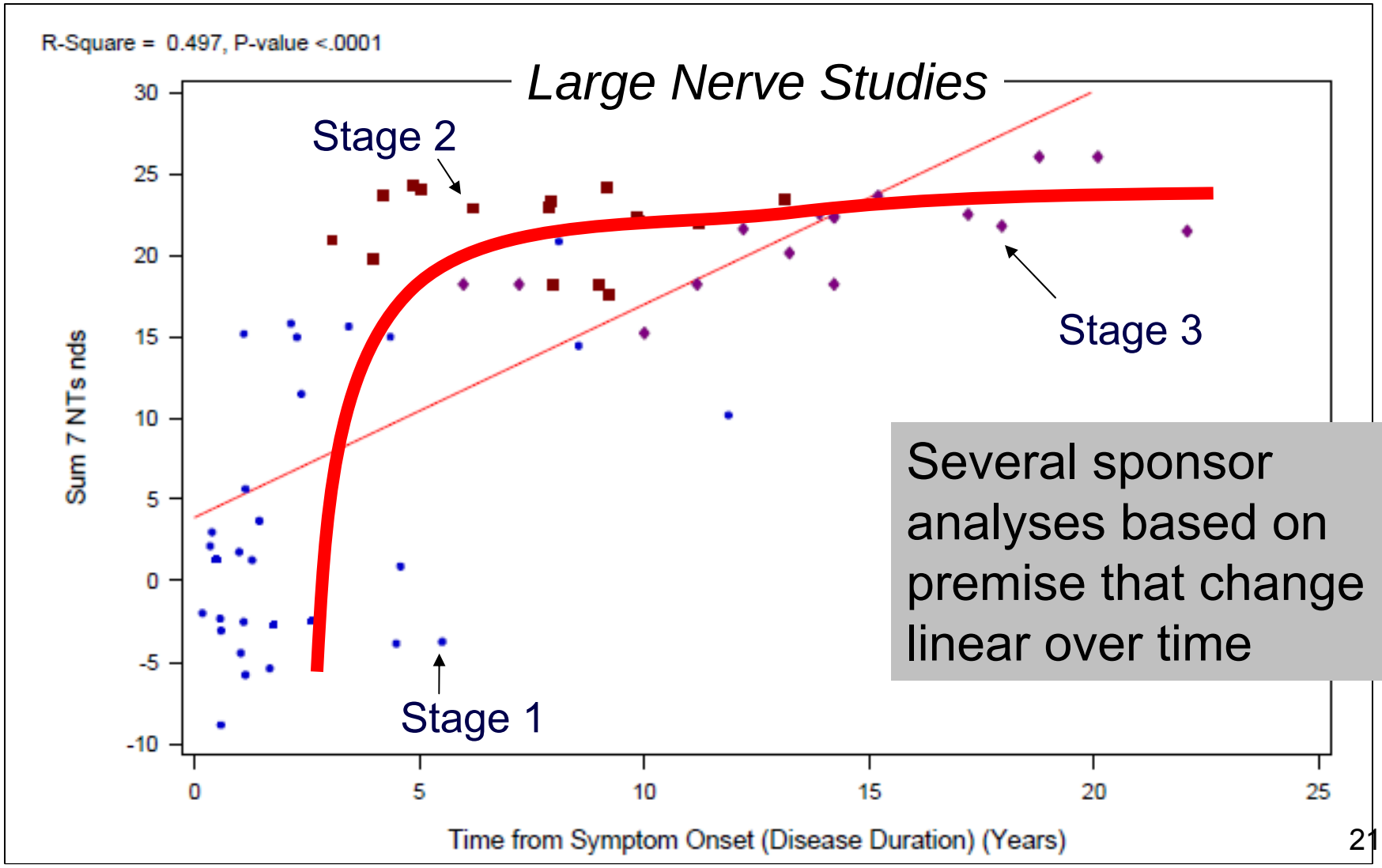
Rate of Change of Efficacy Endpoint May Change with Progression in *Untreated* Patients



note: cross-sectional, not longitudinal data

Figure from Fx1A-OS-001 study report

Some endpoints may be insensitive to further worsening, giving false impression of stabilization



note: cross-sectional, not longitudinal data

Figure from Fx1A-OS-001 study report

Path to Approval

- To be approved, orphan drugs need to show substantial evidence of efficacy
  - 2 positive studies (p-value < 0.05), or
  - 1 very persuasive study + confirmatory evidence

- Also true for Subpart H approval
  - Substantial evidence for an endpoint that does not directly represent intended clinical benefit, but is reasonably likely to predict

Subpart H pathway *applies*

High confidence endpoint changed

+

Endpoint 'reasonably likely' to predict clinical benefit

Subpart H does *not* apply

Drug 'reasonably likely' to affect endpoint

+

High confidence endpoint predicts/is clinical benefit

United States FDA

- Substantial evidence for endpoint other than intended clinical benefit
- Does not allow for approval based on weak evidence of effect on clinical endpoint
- Post-approval studies must confirm clinical benefit

Europe (EMA) 'Exceptional Circumstances'

- Comprehensive data cannot be provided:
  - Rarity of disease, or
  - Present lack of scientific knowledge, or
  - Ethical constraints
- Yearly review of any new information, in particular concerning safety
- Normally, will not lead to completion of full dossier and normal marketing authorization

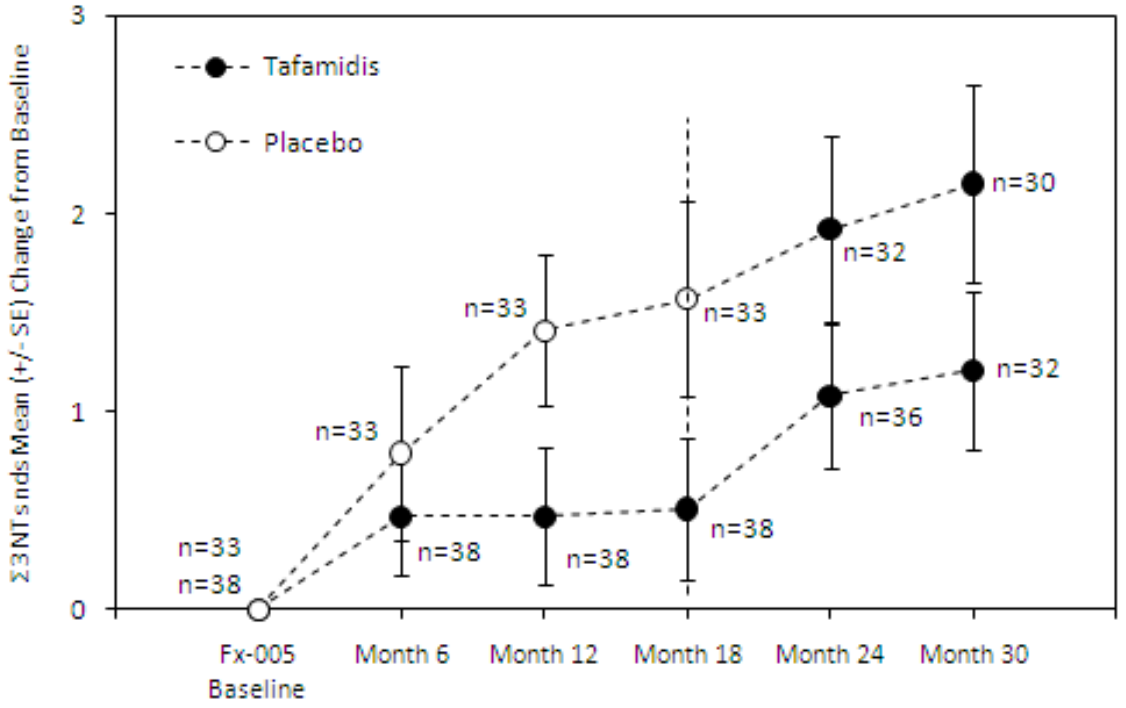
Large Fiber Function as Subpart H Surrogate

- *If* supported by substantial evidence, might ask if reasonably likely to predict clinical benefit
- Nominal p-value 0.06
  - Even before considering problems with multiple-testing and other study weaknesses, a negative finding in usual sense

Small Fiber Function as Subpart H Surrogate

- Nominal p-value 0.005
  - But in setting of multiple testing after negative tests
  - And in study with weaknesses as described

And worsening of treated patients in open-label extension



Figures from sponsor efficacy summary

NIS-LL as Surrogate Endpoint

- Small change in NIS-LL found on exam may not represent clinical benefit perceivable to patient
- A small change in NIS-LL may be a surrogate reasonably likely to predict benefit
- But approval under subpart H would still require substantial evidence for NIS-LL endpoint
  - 2 positive studies (p-value ≤ 0.05), or
  - 1 very persuasive study + confirmatory evidence

TTR Stabilization Assay and 'Reasonably Likely'

- Non-physiological conditions used to measure tafamidis effect on dissociation of tetramer
- Reported 100% stabilization means tetramer dissociation 2x slower; 200% = 3x slower
  - TTR monomers still form

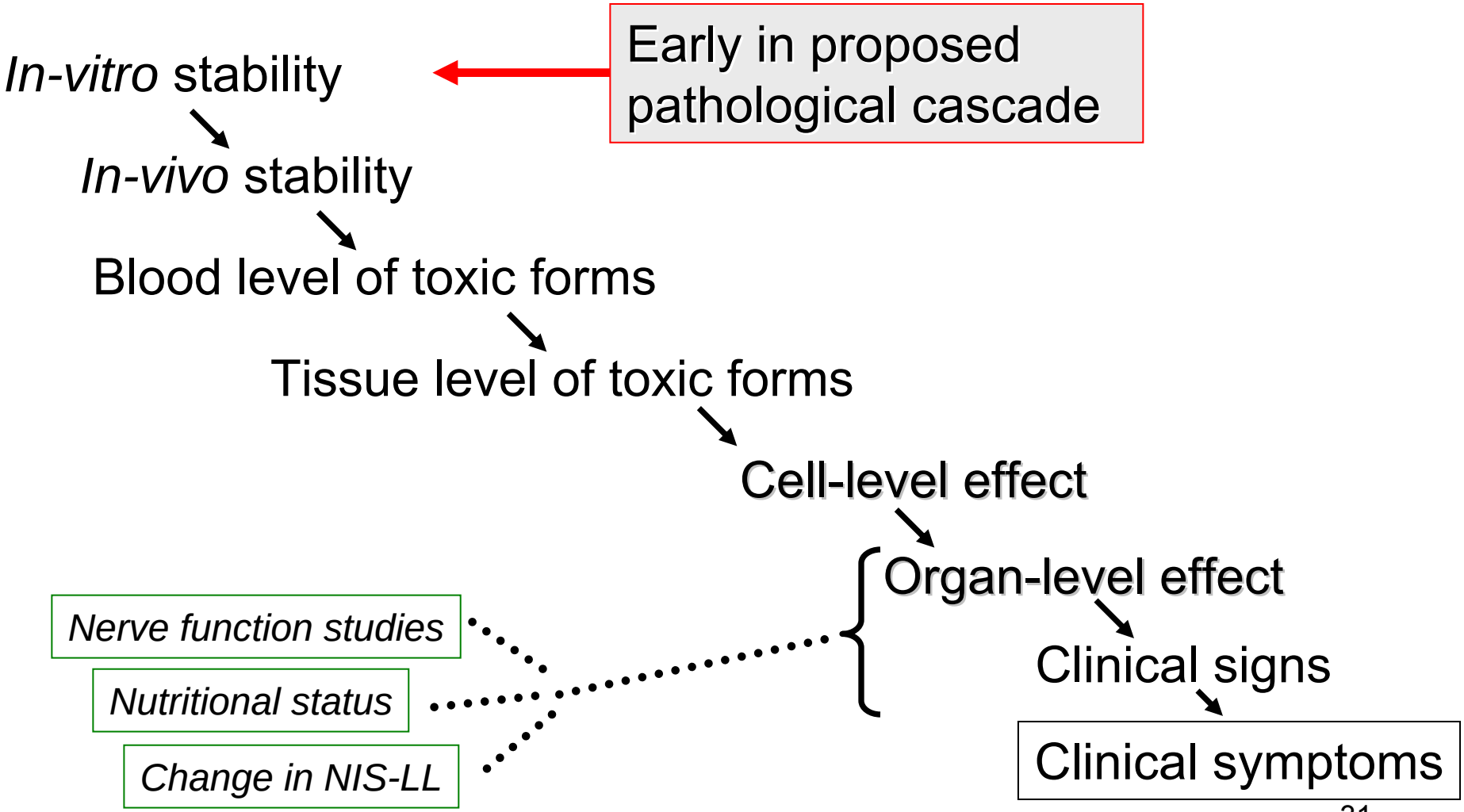
TTR Stabilization and 'Reasonably Likely'

- Factors other than the specific mutation appear to have large effect on penetrance, age of onset, and clinical course of FAP

- Inherited protection by T119M variant:
  - How comparable 'from conception' genetic prevention vs. treat active disease with drug?

- Countless examples of assays not predicting clinical benefit

TTR Stabilization Assay and 'Reasonably Likely'



Path to Approval if More Data Necessary

Options for Study Population

A) V30M FAP, include patients not studied (e.g. Japan)

B) Non-V30M FAP patients

- Knowledge from 005 might allow smaller, shorter study

B) Pre-symptomatic FAP patients

- Population of interest, with no data available
- Address concern that might be necessary to treat earlier

C) Studies in closely related TTR-amyloid diseases

- Familial amyloid cardiomyopathy (FAC)
- Age-related TTR-amyloid cardiomyopathy
- Tens of thousands or more patients affected in U.S.

Options for Study Design

A) Accrual of unexposed patients

B) Randomized withdrawal of patients on tafamidis in current studies or registries

- Minimizes accrual time

C) High vs. low dose / dose-response design

- *Maximum efficacy at 20 mg?*

D) Adaptive design - enhance efficiency

Need for evidence drugs are effective

Need to minimize wait for effective treatment

Expanded Access regulations might be applied in a number of ways

- Treat FAP patients under Expanded Access, and study TTR-Cardiomyopathy patients
- Treat *symptomatic* FAP patients and study pre-symptomatic patients